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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,925	03/11/2004	Glenn Kawasaki	NATH-003	6828

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,925	KAWASAKI ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *2-4,7-17 and 24-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-23-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of claims 1, 5-6, and 18-23 in the reply filed on May 31, 2006 is acknowledged. The traversal is on the ground(s) that there is no unduly burdensome search for all claims in the instant application. This is not found persuasive because different inventions grouped as groups I-III in the previous Office action require different target nucleic acids that are not co-extensive in key word search terms, thus would impose a serious and undue burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Pending Claims

Claims 2-4, 7-17, and 24-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 31, 2006. Accordingly, claims 1-31 are pending, and claims 1, 5-6, and 18-23 are under examination.

Specification

The disclosure is objected to because of the following informalities: The first page of the instant specification contains a blank underlined area for a provisional patent application serial number. Appropriate correction is required.

The disclosure is objected to because of the following informalities: Page 38, line 26 of the instant application contains a blank line except for one word, "accurate". It is unclear whether a piece of disclosure is omitted because the line does not contain a punctuation mark period to indicate the line ends with the word "accurate", and even if the line ends with "accurate", the indicated portion of the disclosure does not read properly. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hsuih et al. (*Journal of Clinical Microbiology,* 1996, also applicant's citation, PTO form 1449A).

Claim 1 is directed to a method of quantifying the amount of a target nucleic acid of less than about 30 nucleotides in length in a sample by contacting the target nucleic acid with at least two oligonucleotides complementary in sequence to the target nucleic acid, followed by ligating

the oligonucleotide/target nucleic acid, which allows determination of the amount of said target nucleic acid in a sample.

In view of *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) and *In re Cortright* 165 F.3d 1353,1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999), the pending claims must be "given their broadest reasonable interpretation consistent with the specification."

Given the broadest reasonable interpretation of the claim language, "less than about 30 nucleotides in length" of claim 1 consistent with the instant specification, "less than about 30 nucleotides in length" will be construed in light of "the target nucleic acid is a RNA that does not exceed about 30 nt" (page 8, line 17-18) and " the length of the duplex typically ranges from about 15 to 30 bp" (page 9, lines 5-6). In view of the foregoing, a target nucleic acid of 30 nucleotides in length legitimately corresponds to a target nucleic sequence of "less than about 30 nucleotides in length".

Given the broadest reasonable interpretation of the claim language consistent with the specification, "ligation domains" of claim 1 or "ligation deoxyribo-oligonucleotides" of claim 18 will be interpreted to mean a nucleic acid complementary sequence that hybridizes to the target sequence such as PCR primer oligonucleotide in light of the instant disclosure, which recites a " PCR primer domain" and "oligonucleotides" as examples of ligation domains (see pages 13-16).

The reference of Hsuih et al. teaches a method for detecting the amount of hepatitis C virus (HCV) RNA in serum by incubating two different oligonucleotides that are 30 nucleotides in length and adjacently complementary to the HCV RNA sequence with the target HCV RNA sequence (underlined portion of Hemiprobe 1 and 2, see Table 1), followed by a step of incubation with T4 DNA ligase to produce a ligated product of oligonucleotide/HCV RNA target

sequence. This final product is then used to serve as a template for a PCR amplification (see Figure 2). Hsuih et al. teach that there is a correlation between the amount of PCR product and the initial number of RNA molecules, thus allowing for a method of quantifying the amount of a target nucleic acid in a sample. Accordingly, all the limitations of the instantly claimed invention are met by Hsuih et al.

Claims 18-20 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Wenz et al. (US 2003/0119004 A1, also applicant's citation, PTO form 1449A, filed on June 14, 2004).

Claims 18-20 and 22 are drawn to a method of quantifying an siRNA in a sample by contacting the sample with at least two oligonucleotides that are complementary to different adjacent domains of said siRNA, which produces a pseudotarget nucleic acid that is amplified via PCR and detecting PCR amplified product to quantify said siRNA in said sample, wherein the said target nucleic acid is a single-stranded RNA (claim 19), double-stranded RNA (claim 20) and said quantifying is relative (claim 22).

In view of *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) and *In re Cortright* 165 F.3d 1353,1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999), the pending claims must be "given their broadest reasonable interpretation consistent with the specification."

Given the broadest reasonable interpretation of the claim language consistent with the specification, "siRNA" of claims 5 and 18-21 will be interpreted to mean any double-stranded molecule containing both sense and antisense sequences in light of the instant disclosure on page 11, which reads "siRNA....contains both sense and antisense sequences that are capable of base-paring between these sequences" (lines 21-23).

The reference of Wenz et al. discloses a method of quantifying the amount of a target nucleic acid in a sample by contacting the sample with at least two oligonucleotides that adjacently hybridize to said target nucleic acid whereby the resultant pseudotarget nucleic acid is amplified via PCR and quantified, wherein said target nucleic acid is single or double-stranded DNA or cDNA or RNA or DNA:RNA hybrid (paragraphs 0062, 0123-0126, and 0230 & Figure 1). It teaches that the amount of target nucleic aid sequence can be quantitated using conventional TaqMan assays (paragraph 0122). It further teaches that the amplification products of the resultant pseudotarget nucleic acid via PCR provide relatively quantitative results when two or more target nucleic acids are assayed relative to each other (paragraph 0268 and Figures 12-13). Therefore, all the structural and functional limitations of the instantly claimed invention are met by the teachings of Wenz et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-6, and 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsuih et al. and Wenz et al. as applied to claims 1, 18-20 and 22 in §102 rejections above, further in view of Eglen (US 2006/0105377 A1) and Hannon (*Nature,* 418: 244-251, 2002).

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/457,527, fails to provide adequate description in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The above prior-filed application does not disclose "shRNA molecule" of claims 6 and 21. Accordingly, claims 6 and 21 are not entitled to the benefit of the prior application, and thus the filing date of Application No. 60/532,699 (December 24, 2003) will be the effective filing date for claims 6 and 21.

If applicant believes that the claimed subject matter in claims 6 and 21 of the instant application is disclosed in the prior-filed applications to which applicant claims the benefit under 35 U. S. C. 119(e), applicant is advised to point out the particulars in response to this Office action.

Claim 1, 5-6, and 18-23 are drawn to a method of quantifying the amount of a target nucleic acid of less than 30 nucleotides in a sample by contacting the sample with at least two

complementary oligonucletoides that produce an oligonucleotide/target nucleic acid complexes via ligation and the resultant pseudotarget nucleic acid is amplified via PCR and quantified, wherein the said target nucleic acid is an siRNA (claims 5, 18-20) an shRNA (claims 6 and 21) and said quantifying is relative (claim 22) or absolute (claim 23).

In view of *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) and *In re Cortright* 165 F.3d 1353,1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999), the pending claims must be "given their broadest reasonable interpretation consistent with the specification."

Given the broadest reasonable interpretation of the claim language consistent with the specification, the phrase "quantitating is absolute" of claim 23 will be interpreted to mean quantifying through referencing to control nucleic acid(s) or quantifying only a single target nucleic acid based on the description of absolute quantification on page 9 of the instant specification.

As described above for §102 claim rejections above, both Hsuih et al. and Wenz et al. teach a method of quantifying the amount of a target nucleic acid in a sample by contacting the sample with at least two complementary oligonucleotides that produce an oligonucleotide/target nucleic acid complexes via ligation and the resultant pseudotarget nucleic acid is amplified via PCR and quantified, wherein said target nucleic acid is double-stranded RNA, wherein the quantifying can be performed by relative quantification measurements. Since Hsuih et al. teach a method of quantifying a single target nucleic acid in a sample, they teach an absolute quantification method. Neither teaches a method of quantifying an shRNA in a sample.

The reference of Eglen teaches a method of absolute quantification of an shRNA in cells, wherein specific shRNA knockdown activity is measured in comparison to a control, non-specific shRNA sequence (paragraphs 12, 60, and 68-69).

The reference of Hannon teaches that short hairpin RNAs can be used to manipulate gene expression just like siRNAs (page 250).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to quantify the amount of a target nucleic acid of 30 nucleotides of Hsuih et al., especially double-stranded RNA of Wenz et al. and shRNA of Eglen by means of a relative quantifying method of Wenz et al. or an absolute quantifying method of Hsuih et al. One of ordinary skill in the art would have been motivated to combine the teachings of the prior art with a reasonable expectation of success because the method of quantifying the amount of a nucleic acid of 30 nucleotides and double-stranded RNAs via ligation followed by amplification by PCR has been previously taught and utilized by both Hsuih et al. and Wenz et al, which would allow the skilled artisan to correlate the amount of PCR product with the amount of RNA molecule present in a sample. Further, the skilled artisan would have been motivated to quantify shRNA in place of siRNA because shRNA has been known to be a functional variant of siRNA by Hannon, thus the skilled artisan would utilize the method of quantifying shRNA when shRNA was employed to manipulate gene expression in a sample. In light of the above, the skilled artisan would have replaced the method of quantifying the amount of a double-stranded RNA of Wenz et al. with the method of quantifying the amount of shRNA of Eglen with a reasonable expectation of success in view of the combined teachings of the prior art. Accordingly, the instantly claimed invention of claims 1, 5-6, and 18-23 taken as a whole is *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Dana Shin
July 5, 2006